CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

DICLORAN/DICHLORAN

Chemical Code # 000081, Tolerance # 00200
SB 950 # 141

Original date: 7/00/93
Revised date

I. DATA GAP STATUS

Chronic toxicity, rat:	## Data gap, inadequate study, no adverse effect indicated
Chronic toxicity, dog:	## Data gap, inadequate study, no adverse effect indicated
Oncogenicity, rat:	## Data gap, inadequate study, no adverse effect indicated
Oncogenicity, mouse:	## No data gap, no adverse effect indicated
Reproduction, rat:	## Data gap, inadequate study, no adverse effect indicated
Teratology, rat:	No data gap, no adverse effect indicated
Teratology, rabbit:	## Data gap, inadequate study, no adverse effect indicated
Gene mutation:	## No data gap, adverse effect indicated

Chromosome effects: ## Data gap, inadequate study, possible adverse effect indicated

DNA damage: ## No data gap, no adverse effect indicated

Neurotoxicity: Not required at this time.

Toxicology one-liners are attached.

All record numbers through 116087 were examined (7/2/93).
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study/worksheet on file but not yet given a final review. A preliminary one-liner (##) is temporarily entered in the Toxicology Summary. The temporary one-liner and data gap status is subject to change pending the final review.
File name: T930700
Original: Kishiyama, 7/00/93.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

CHRONIC TOXICITY, RAT

028 45506, "T26 DCNA: U-2069 - Safety Evaluation by Oral Administration to Rats and Dogs for 104 Weeks", (M.W. Woodard, K.O. Cockrell, and G. Woodard, Woodard Research Corporation, U2069, 2/3/64). U-2069 was admixed with the feed at concentrations of 0, 20, 100 or 3000 ppm and fed to 5 rats/sex/group for 13 weeks and 30 rats/sex/group for 104-107 weeks. Body weight was reduced 25-28% for the high dose group; hematology and hematocrit values were reduced for high dose females and especially for males; the liver, kidney and testes weight was increased slightly for high dose males; and the incidence of glycogen depletion, hepatic cell enlargement, basophilia of the cytoplasm and necrobiotic hepatic cells were distinctly increased for the high dose group. NOEL = 100 ppm/day. UNACCEPTABLE. (Kishiyama, 6/14/93).

042 116080. Supplement to 045506.

028 045508. Addendum to 45506.

042 116075. Duplicate of 045508.

042 116074. Duplicate of 28 044506 and 045507.

CHRONIC TOXICITY, DOG

042 45507, "T26 DCNA: U-2069 - Safety Evaluation by Oral Administration to Rats and Dogs for 104 Weeks", (M.W. Woodard, K.O. Cockrell, and G. Woodard, Woodard Research Corporation, U2069, 2/3/64). U-2069 admixed with the feed at concentrations of 0, 20, 100 or 3000 ppm and

fed to 4 dogs/sex/group. One dog/sex/group was sacrificed at week 14 and 3/sex/group at week 107. UNACCEPTABLE. Not Upgradeable (major deficiencies). (Kishiyama, 6/15/93).

042 116080. Supplement to 045506.

042 116074. Duplicate of 28 044506 and 045507.

ONCOGENICITY, RAT

043 116081, "T59 DCNA: Two-Year Feeding Trial in Rats on Dichloran (2,6-Dichloro-4-nitroaniline) (MRID No. 00086903)", (B. Lessel, Boots Pure Drug Co., Ltd., United Kingdom, 1974). Dichloran was incorporated with the feed at concentrations of 0 and 1000 ppm and fed to 25 Boots-Wistar rats/sex/group for two years. No significant treatment related effects were reported. UNACCEPTABLE. Not upgradeable (major deficiencies). (Kishiyama, 6/24/93).

ONCOGENICITY, MOUSE

** 044 116085, "T104A Technical Dicloran: Oncogenicity Study in the Mouse", (B.A. Mallyon and L.P. Markham, Schering Agrochemicals Limited, TOX/86006, 1/6/89). Technical Dicloran (CR 20642/3) 97.2%, a fine yellow powder was admixed with the feed at concentrations of 0, 50, 175 or 600 ppm and fed to 50 CD-1 mice/sex/group for 80 weeks. No evidence of oncogenicity; Onco NOEL = 600 ppm/day. Increased incidence of hepatotoxicity (male & female), erythropoesis in the spleen (males) and cystic endometrial hyperplasia of the uterus; and liver weight was increased; Systemic NOEL = 142-173 ppm/day (dicloran at 175 ppm in feed was unstable). ACCEPTABLE. (Kishiyama, 6/9/93).

045 116087. Filed under 44 116085.832. EPA review of mouse onco study. EPA classified this study as core guideline. Oncogenicity: negative. LEL = 175 ppm (30.0 mg/kg/day and NOEL = 600 ppm (102.7 mg/kg/day.

(Note: analytical data on diets was not available for EPA review).

043 116083. Filed under 44 116085.832. Publication (Journal of National Cancer Institute, April 30, 1969). "Bioassay of Pesticides and Industrial Chemicals for Tumorigenicity in Mice: A Preliminary Note", (J.R.M. Innes, B.M. Ulland, M.G. Valerio, L. Petrucelli, L. Fishbein, E.R. Hart and A.J. Pallotta, Bionetics Research Laboratories, Inc., Litton Industries and R.R. Bates, H.L. Falk, J.J. Gart, M. Klein, I. Mitchell and J. Peters, National Cancer Institute. Mice were administered the test compound by intubation beginning at the age of 7 days to weaning (4 weeks old) and thereafter given compound treated feed up to the age of 18 months. Eleven of 120 compounds induced a significant elevation in the incidence of tumors, 20 need further investigation and 89 gave no indication of tumorigenicity. Botran (215 mg/kg or 603 ppm) was on the list of 89 compounds. (No worksheet, Kishiyama, 6/9/93).

045 116086. Filed under 44 116085.832. T104A Dicloran: Determination of Dicloran Dietary Concentration for an Oncogenicity Study in the Mouse, (J.H.M. Bright, Schering Agrochemicals Limited, RESID87/127, 7/29/88). See (record 44 116085) IV. STUDY DESIGN AND CONDUCT EVALUATION, item 2, **Analysis of dosing material (stability, homogeneity, compound content)**. No worksheet. (Kishiyama, 6/9/93).

REPRODUCTION, RAT

028 045510; 200-008 919617, "U-2069 Effect on Reproductive Capacity Through Three Generations in the Rat. Final Report", (B.J. Lobdell and C.D. Johnston, Woodard Research Corporation, DCNA/# T 35, 3/15/65). U-2069 (Botran), purity not stated, incorporated with the feed at concentrations of 0 and 100 ppm and fed to three generations (2 litters/generation) of 20 albino rats/sex/group/generation). Major variance from guidelines and insufficient information. UNACCEPTABLE. Not upgradeable. (Kishiyama, 6/22/93).

042 116078. Summary of 919617.

TERATOLOGY, RAT

** 023 11287, "U-2069: A Segment II Teratology Study in the Rat (Botran), (Upjohn Co., 9610/82/7263/005, 7/26/80). Dichloran technical (>93% purity), administered at concentrations of 0 (methylcellulose), 100, 200 or 400 mg/kg/day to 24 - 20 pregnant Sprague-Dawley rats/group. Maternal weight gain decrease was dose related and observed for all groups; Maternal NOEL = <100 mg/kg/day. Fetal weight was decreased; embryonic death was dose related; skeletal and visceral variations was borderline for the mid and high dose groups. Developmental NOEL = 100 mg/kg/day. ACCEPTABLE (minor variance). (J. Schreider, 4/29/89).

TERATOLOGY, RABBIT

060 145609 (Pilot Study): Wilcox, S. and S.J.Barton. Dicloran Toxicity Study in Rabbits. Inveresk Research International, IRI Project No. 491294. February 26, 1996. Dicloran Technical, purity 98.8-98.3% was administered via gavage at concentrations of 0, 8, 20 or 50 mg/kg to 16 mated female New Zealand White rabbits/group on Days 6 through 18 of gestation. No adverse developmental/ reproductive effects reported. A slight reduction in maternal weight gain is reported for mid and high dose groups. Body weight increase during treatment (days 6-18) was .33 (8%), .34 (8%), .23 (6%) and .26 (7%)kg for the control, low, mid and high dose groups, respectively. [No work sheet]. (Kishiyama, 7/8/96).

28 045511, "Somers Test in the Albino Rabbit", (F.X. Wazeter, International Research Development Corporation, DCNA /# T38, 2/10/66). Botran, purity not given, was incorporated with the feed at concentrations of 0, 100 or 1000 ppm and fed to 11, 12 or 14 pregnant female New Zealand rabbits/group for nine days (Days 8 through 16 of gestation). No adverse treatment related effects on parental females, reproduction or fetuses/pups reported. UNACCEPTABLE. Not upgradeable (major variance from guidelines; insufficient information). (Kishiyama, 6/22/93).

GENE MUTATION

** **036 069790**, "T103 Technical Dicloran: Ames Bacterial Mutagenicity Test", (E. Jones and L.A. Fenner, Huntingdon Research Centre/Schering Agrochemicals Limited, England Tox/87/199-85, July 1987). Dicloran technical 97.5% purity, was tested for mutagenicity potential on *Salmonell typhimurium* tester strains TA 1535, TA1537, TA1538, TA98 and TA100, with and without metabolic activation (S-9 Mix). Exposure time was for 72 hours at 37:C. **Adverse effect:** an increase in revertant colonies was observed in two tests with tester strains TA1538 and TA98 in the presence and absence of metabolic activity and with TA 100 in the absence of metabolic activity. ACCEPTABLE. (Kishiyama, 6/30/93).

CHROMOSOME EFFECTS

036 069791, "T105 Technical Dicloran: Metaphase Chromosome Analysis of Human Lymphocytes Cultured In Vitro", (J. Allen, P.C. Brooker and V. M. Gray, Huntingdon Research Centre, England, TOX/87/199-188, 7/30/87/1/20/88. Technical Dicloran, purity 97.5%, at concentrations of 0, 2, 10, or 20 µg/ml was evaluated with and without metabolic activation (S-9 Mix) for potential inducement of chromosome aberration in cultured human lymphocytes. **Chromosome aberration was slightly elevated, dose related and statistically significant.** However, reported as not indicative of clastogenic activity historically. No repeat test. UNACCEPTABLE. Upgradeable (dosing material analysis). (Kishiyama, 7/2/93;).

DNA DAMAGE

** 036 069792,"T108 Technical Dicloran: Assessment of Unscheduled DNA Synthesis Using Rat Hepatocyte Cultures", (D. McBride and D.B. McGregor, Inveresk Research International, IRI Project No. 736642, 4/21/88). Technical Dicloran, purity 97.5%, at concentrations of 3, 4, 5, 6, 7, 8, 9, or 10 $\mu g.ml^{-4}$) was assessed for unscheduled DNA synthesis on rat hepatocytes. Two tests with dicloran treatments on rat hepatocytes showed no evidence of induction of unscheduled DNA synthesis. ACCEPTABLE (with some deficiencies). (Kishiyama, 7/6/93).

NEUROTOXICITY

Not required at this time.